US5990346: Prostaglandins and processes for produc

Inventor(s): **Kataoka; Kenichiro** , Tokyo, Japan
Minoshima; Toru , Yamaguchi, Japan
Shiota; Tatsuki , Tokyo, Japan
Tsutsumi; Takaharu , Tokyo, Japan
Hada; Takahiko , Tokyo, Japan
Tanaka; Hiroko , Tokyo, Japan
Morita; Takuya , Tokyo, Japan
Endo; Noriaki , Tokyo, Japan

Applicant(s): **Teijin Limited**, Osaka, Japan
Other patents from TEIJIN LIMITED (approx. 1139)

Issued/Filed Dates: **Nov. 23, 1999** / Feb. 26, 1997

Application Number: **US1997000793486**

IPC Class: C07C 405/00; C07C 069/74; A61K 031/557;

Class: 562/503; 549/422; 554/117; 554/214; 560/121; 514/573;

Field of Search: **562/503 435/063 549/422 554/117,214 560/121 514/573**

Abstract: A prostaglandin having formula (I), (II), or (III): *[Figure]* a process of production thereof, and inhibitors of cell migration caused by chemokines containing (I) or (II) as an active ingredient.

Attorney, Agent, or Firm: **Sughrue, Mion, Zinn, Macpeak & Seas, PLLC;**

Primary/Assistant Examiners: **Hutzell; Paula K.**; Worrall; Timothy A.

U.S. References: (No patents reference this one)

Patent	Issued	Inventor(s)	Applicant(s)	Ti
US4363817	12 /1982	Biddlecom	Miles Laboratories, Inc.	Enol acylate analogs of E

First Claim: Show all 13 claims

We claim:

1. A prostaglandin having the formula (I): *[Figure]* wherein R^1 indicates a C_1 to C_{10} str group, a cyano group, a formyl group, a carboxyl group, a C_1 to C_5 alkyloxycarbonyl gro substituted with one or more halogen atoms or one or more substituted or unsubstituted

- Z indicates a hydrogen atom or OR^2,
- R^2 and R^3 are the same or different and indicate a hydrogen atom, a tri C_1 to C_7 h

with the oxygen atom of a hydroxy group,

- R^4 indicates a C_1 to C_8 straight chain or branched alkyl group, a C_2 to C_8 straight or branched alkynyl group, a substituted or unsubstituted phenyl group, a substitut chain or branched (C_1 to C_5 alkyl group, C_2 to C_5 alkenyl group, or a C_2 to C_5 alky a substituted or unsubstituted phenyl group, a substituted or unsubstituted phenox group, or a substituted or unsubstituted heterocyclic group,
- Y indicates a C_1 to C_5 straight chain or branched alkyl group or CO_2 R^5,
- R^5 indicates a hydrogen atom, a C_1 to C_{10} straight chain or branched alkyl group, one equivalent cation,
- X indicates a methylene group or an oxygen atom,
- W indicates a sulfur atom, a sulfynyl group or a methylene group, and
- the bond represented by a solid line together with a broken line indicates a double
- an enantiomer thereof or any mixture of enantiomers at any ratio.

Background/Summary: Show background/summary

Drawing Descriptions: Show drawing descriptions

Description of Preferred Embodiments:

EXAMPLES

The present invention will be further verified below according to the Examples, but the these Examples.

Example 1

Synthesis of methyl (11R,12R,13E,15S,17R)-9-trifluoromethanesulfonyloxy-11,15-bis(tert-butyldimethylsiloxy

(1E,3S,5R)-1-iodo-3-(tert-butyldimethylsiloxy)-5-methyl-1-nonene (951 mg, 2.4 mmol) tert-butyllithium (1.54 mol/L, 3.12 mL, 4.8 mmol) was added. This was agitated at -78° C (I) (347 mg, 2.4 mmol) and hexamethylphosphorus triamide (872 µl, 4.8 mmol) in ether (give copper reagent. To the obtained copper reagent was drop-wise added (4R)-tert-butyldimethylsiloxy-2-(6-methoxycarbonylhexyl)-2-cyclopenten-1-one (709 mg, mixture was agitated at -78° C. for 15 minutes, then the reaction temperature was raised conjugate adduct. To the resultant conjugate adduct was added at -30° C. N-phenyltrifluc tetrahydrofuran (6 mL). This was agitated for 15 hours while raising the reaction tempera poured into saturated ammonium sulfate (100 mL) to end the reaction. The mixture was ether and the extract was combined with the organic layer, then dried over anhydrous m reduced pressure, then was purified by silica gel column chromotography (2 to 5% ethyl (11R,12R,13E,15S,17R)-9-trifluoromethanesulfonyloxy-11,15-bis (tert-butyldimethylsilox ^{1}H-NMR (270 MHz, .delta.ppm, $CDCl_3$): 0.00, 0.01, 0.05 (s, 12H), 0.8-0.9 (m, 6H), 0.87 (s (t, J=7.6 Hz, 2H), 2.46 (d, J=15.8 Hz, 1H), 2.91 (dd, J=6.9 & 16.2 Hz, 1H), 3.04 (d, J=8.9 15.5 Hz, 1H), 5.56 (dd, J=5.9 & 15.5 Hz, 1H),

Example 2

Synthesis of methyl (11R,12R,13E,15S,17R)-9-trifluoromethanesulfonyloxy-11,15-dih

As a byproduct of the reaction of Example 6, methyl (11R,12R,13E,15S,17R)-9-trifluoromethanesulfonyloxy-11,15-dihydroxy-17,20-dimethylp ^{1}H-NMR (270 MHz, .delta.ppm, $CDCl_3$): 0.8-1.0 (m, 6H), 1.1-2.0 (m, 17H), 2.1-2.4 (m, 2 2.95 (dd, J=7.3 & 15.8 Hz, 1H), 3.10 (dd, J=3.6 & 8.9 Hz, 1H), 3.67 (s, 3H), 4.1-4.3 (m, 2 Hz, 1H)

Example 3

Synthesis of methyl (11R,12S,13E,15S,17R)-9-trifluoromethanesulfonyloxy-11,15-bis(tert-butyldimethylsiloxy

(1E,3S,5R)-1-iodo-3-(tert-butyldimethylsiloxy)-5-methyl-1-nonene (476 mg, 1.2 mmol) tert-butyllithium (1.54 mol/L, 1.56 mL, 2.4 mmol) was added. This was agitated at -78° C (I) (174 mg, 1.2 mmol) and hexamethylphosphorus triamide (436 µl, 2.4 mmol) in ether (give copper reagent. To the copper reagent thus obtained was drop-wise added (4R)-tert-butyldimethylsiloxy-2-(5-methoxycarbonylpentylthio)-2-cyclopenten-1-one (373 mixture was agitated at -78° C. for 15 minutes, then the reaction temperature was raised conjugate adduct. To the obtained conjugate adduct was added at -30° C. N-phenyltrifluc tetrahydrofuran (5 mL). This was agitated for 15 hours while raising the reaction tempera poured into saturated ammonium sulfate (65 mL) to end the reaction. The mixture was s The extract was combined with the organic layer, then dried over anhydrous magnesium pressure, then was purified by silica gel column chromotography (2 to 5% ethyl acetate/h (11R,12S,13E,15S,17R)-9-trifluoromethanesulfonyloxy-11,15-bis(tert-butyldimethylsiloxy 52%). ^{1}H-NMR (270 MHz, .delta.ppm, $CDCl_3$): 0.03, 0.05, 0.06 (s, 12H), 0.8-0.9 (m, 6H) J=7.4 Hz, 2H), 2.4-2.9 (m, 3H), 2.97 (dd, J=6.3 & 16.2 Hz, 1H), 3.16 (d, J=7.9 Hz, 1H), 3 1H), 5.64 (dd, J=5.4 & 15.7 Hz, 1H)

Example 4

Synthesis of methyl (11R,12S,13E,15S)-9-trifluoromethanesulfonyloxy-11,15-bis(tert-butyldimethylsiloxy)-16-

[Figure]

(1E,3S)-1-iodo-3-(tert-butyldimethylsiloxy)-4-phenyl-1-butene (699 mg) in ether (4 mL) 2.40 mL) was added. This was agitated at -78° C. for 1 hour. Further, to this were added triamide (654 µl) in ether (10 mL). This was agitated at -78° C. for a further 1 hour to giv drop-wise added (4R)-tert-butyldimethylsiloxy-2-(5-methoxycarbonylpentylthio)-2-cyclope reaction mixture was agitated at -78° C. for 1 hour, then the reaction temperature was ra obtain a conjugate adduct. To the obtained conjugate adduct was added at -40° C. N-phe tetrahydrofuran (13 mL). The solution was agitated for 1 hour, while raising the reaction t was poured into saturated ammonium sulfate (100 mL) to end the reaction. The mixture ether and the extract was combined with the organic layer, then dried over anhydrous m reduced pressure, then was purified by silica gel column chromotography (3 to 4% ethyl (11R,12S,13E,15S)-9-trifluoromethanesulfonyloxy-11,15-bis(tert-butyldimethylsiloxy)-16- (983 mg, 86%). ^{1}H-NMR (270M Hz, .delta.ppm, $CDCl_3$): -0.25 (s, 3H), -0.09 (s, 3H), 0.0 (m, 6H), 2.31 (t, J=7.3 Hz, 3H), 2.4-2.6 (m, 2H), 2.65-2.8 (m, 3H), 2.93 (ddd, J=1.6 & 6.2 4.0-4.03 (m, 1H), 5.28 (dd, J=4.9 & 11.6 Hz, 1H), 5.43 (ddd, J=1.0 & 8.2 & 15.5 Hz, 1H),

Example 5

Synthesis of methyl (11R,12R,13E,15S,17R)-9-methyl-11,15-bis(tert-butyldimethylsilo

To tetrakistriphenylphosphinepalladium prepared in advance in the system from tris(di and triphenylphosphine (105 mg, 0.4 mmol) were added methyl(11R,12R,13E,15S,17R)-9-trifluoromethane-sulfonyloxy-11,15-bis(tert-butyldimeth mmol) in a 1,2-dichloroethane (5 mL) solution and 2M trimethylaluminum in hexane (0.3 temperature. Ether was added to dilute the reaction solution, then the solution was poure extracted with ether from the mixture. The extract was washed with brine, then was drie concentrated under reduced pressure, then was purified by silica gel column chromotogr methyl(11R,12R,13E,15S,17R)-9-methyl-11,15-bis(tert-butyldimethylsiloxy)-17,20-dimeth methyl(11R,12R,13E,15S,17R)-9-trifluoromethanesulfonyloxy-11,15-bis(tert-butyldimeth mg). The NMR data for the mixture was measured, but could not be analyzed. This mixt further purification.

Example 6

Synthesis of methyl (11R,12R,13E,15S,17R)-9-methyl-11,15-dihydroxy-17,20-dimethy

To a solution of ice-cooled acetonitrile (2 ml) and pyridine (0.2 mL) was added hydrog mixture (174 mg) containing methyl (11R,12R,13E,15S,17R)-9-methyl-11,15-bis(tert-but pyridine (0.2 mL). The ice bath was removed and the solution was agitated for 15 hours solution was poured into a mixture of ethyl acetate and a saturated aqueous solution of s extracted from this mixed solution with ethyl acetate. The extract was washed with brine,

was concentrated under reduced pressure, then was purified by silica gel column chromc to thin layer chromotography for separation (ethyl acetate:hexane=4:1) to obtain methyl (11R,12R,13E,15S,17R)-9-methyl-11,15-dihydroxy-17,20-dimethylprosta-8,13-dienoate ((11R,12R,13E,15S,17R)-9-trifluoromethanesulfonyloxy-11,15-dihydroxy-17,20-dimethylp Hz, .delta.ppm, $CDCl_3$): 0.8-1.0 (m, 6H), 1.1-1.9 (m, 17H), 1.64 (d, J=0.7 Hz, 3H), 2.0-2. Hz, 1H), 3.04 (d, J=7.3 Hz, 1H), 3.66 (s, 3H), 4.0-4.2 (m, 1H), 4.1-4.3 (m, 1H), 5.40 (dd, C-NMR (67.5 MHz, .delta.ppm, $CDCl_3$): 14.0, 14.1, 19.6, 22.9, 25.9, 26.3, 27.5, 28.9, 29. 67.7, 129.9, 131.5, 135.0, 135.2, 174.3

Example 7

Synthesis of methyl (11R,12S,13E,15S,17R)-9-methyl-11,15-bis(tert-butyldimethylsilo

To tetrakistriphenylphosphinepalladium prepared in advance in the system from tris(di and triphenylphosphine (210 mg, 0.8 mmol) were added methyl (11R,12S,13E,15S,17R)-9-trifluoromethanesulfonyloxy-11,15-bis(tert-butyldimethylsiloxy 0.546 mmol) in 1,2-dichloroethane (5 mL) and 2M trimethylaluminum in hexane (0.423 n temperature. Ether was added to dilute the reaction solution, then the solution was poure extracted with ether from the mixture. The extract was washed with brine, then was driec concentrated under reduced pressure, then was purified by silica gel column chromotogr (11R,12S,13E,15S,17R)-9-methyl-11,15-bis(tert-butyldimethylsiloxy)-17,20-dimethyl-7-th MHz, .delta.ppm, $CDCl_3$): 0.03, 0.05 (s, 12H), 0.8-0.9 (m, 6H), 0.87 (s, 9H), 0.88 (s, 9H), J=7.9 Hz, 1H), 3.66 (s, 3H), 4.0-4.2 (m, 2H), 5.34 (dd, J=8.9 & 15.5 Hz, 1H), 5.52 (dd, J=

Example 8

Synthesis of methyl (11R,12S,13E,15S,17R)-9-methyl-11,15-dihydroxy-17,20-dimethy

To a solution of ice-cooled acetonitrile (2 mL) and pyridine (0.2 mL) was added hydroc methyl(11R,12S,13E,15S,17R)-9-methyl-11,15-bis(tert-butyldimethylsiloxy)-17,20-dimetl pyridine (0.2 mL). The ice bath was removed and the solution was agitated for 15 hours, solution was poured into a mixture of ethyl acetate and saturated aqueous sodium hydro this mixed solution with ethyl acetate. The extract was washed with brine, then dried ove concentrated under reduced pressure, then was purified by silica gel chromotography (3((11R,12S,13E,15S,17R)-9-methyl-11,15-dihydroxy-17,20-dimethyl-7-thiaprosta-8,13-dier $CDCl_3$): 0.8-0.9 (m, 6H), 1.1-1.7 (m, 15H), 1.82 (d, J=1.3 Hz, 3H), 2.3-2.8 (m, 4H), 2.31 (1H), 4.1-4.3 (m, 1H, 5.50 (dd, J=7.9 & 15.2 Hz, 1H), 5.61 (dd, J=6.3 & 15.5 Hz, 1H)

Example 9

Synthesis of (11R,12S,13E,15S,17R)-9-methyl-11,15-dihydroxy-17,20-dimethyl-7-thia

To methyl (11R,12S,13E,15S,17R)-9-methyl-11,15-dihydroxy-17,20-dimethyl-7-thiapr was added pH 8 phosphate buffer (10 mL). To this was further added esterase containinç 100 µl). This was agitated at room temperature for 15 hours. To the reaction solution wa Further, the solution was made saturated by ammonium sulfate, then the desired produc with brine, then was dried over anhydrous sodium sulfate. The solution was concentratec chromotography for separation (development solution: ethyl acetate) to obtain (11R,12S,13E,15S,17R)-9-methyl-11,15-dihydroxy-17,20-dimethyl-7-thiaprosta-8,13-dier $CDCl_3$): 0.8-1.0 (m, 6H), 1.1-1.7 (m, 15H), 1.82 (s, 3H), 2.2-2.8 (m, 4H), 3.1-3.2 (m, 1H), J=6.4 & 15.3 Hz, 1H)

Example 10

Synthesis of methyl (11R,12S,13E,15S,17R)-9-methyl-11,15-bis(tert-butyldimethylsilox